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EXAMINER	
WHISENANT, ETHAN C	

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1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	**Application No.** 10/680,277	**Applicant(s)** TRAN, NATHANIEL TUE	
	Examiner Ethan Whisenant, Ph.D.	**Art Unit** 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 MAR 04, 11 MAY 04 and 15 FEB 05*.
2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-78* is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *39-78* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☒ The drawing(s) filed on *07 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☐ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Non-Final Action

1. The applicant's Preliminary Amendments filed 12 MAR 04, 11 MAY 04 and 15 FEB 05 have been entered in- part, see paragraph 2 below. Following the entry of the Preliminary claim amendments, **Claim(s) 39-78** is/are pending.

SUBSTITUTE SPECIFICATION

2. The substitute specification filed 12 MAR 04, has not been entered because it does not conform to 37 CFR 1.125(b) and/or (c) because: **a statement that the substitute specification contains no new matter has not been supplied.**

A statement that the substitute specification filed 12 MAR 04 **contains no new matter is** required pursuant to 37 CFR 1.125(b).

35 USC § 112- 2ND PARAGRAPH

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

CLAIM REJECTIONS under 35 USC § 112- 2ND PARAGRAPH

4. **Claim(s) 52-53, 55-56, 58-69** is/are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim(s) 52 is/are vague and indefinite because of the phrase "selectively quantified by exploiting the difference in half -life between said first radioactive isotope and said second radioactive isotope." The metes and bounds of this limitation cannot be determined. This rejection can be overcome by positively reciting the step(s) involved in said "exploiting."

Claim(s) 53 is/are vague and indefinite because of the phrase "selectively quantified by exploiting the difference in radiation energy between said first radioactive isotope and said second radioactive isotope." The metes and bounds of this limitation cannot be determined. This rejection can be overcome by positively reciting the step(s) involved in said "exploiting."

Claim 58 is indefinite because there is no nexus between the preamble and the claim steps. Claim 58 in its preamble direct to a method which is to accomplish a particular goal. However, none of the claim steps states that this goal is accomplished. For clarity, claimed methods should recite that the purpose of the method has been attained (i.e. provide a nexus between the preamble and the claim steps).

35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that may form the basis for rejections set forth in this Office action:

> A person shall be entitled to a patent unless --
>
> **(a)** the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> **(b)** the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> **(e)** the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
> or
> **(e)** the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

6. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

CLAIM REJECTIONS UNDER 35 USC § 102

7. **Claim(s) 39, 43, 46, 50, 54, 57, 70-72** is/are rejected under 35 U.S.C. 102(b) as being anticipated by Shuber et al. [US 6,203,993 (2001)].

Claim 39 is drawn to a method of analysis which comprises three steps. To begin, molecules in a first sample are labeled with a first radioactive isotope. Then, molecules in a second sample are labeled with a second radioactive isotope that is different from said first radioactive isotope. Finally said first sample and said second sample are mixed together

Shuber et al. teach a method of analysis comprising the three steps recited in Claim 39. See, at least, for example, Claim 1.

Claim 43 is drawn to an embodiment of Claim 39 wherein the method further comprises two additional steps, namely, quantifying said first radioactive isotope in said mixture and said second radioactive isotope in said mixture.

Shuber et al. teach this/these limitation(s). See, at least, for example, Column 4, beginning at about line 52.

Claim 46 is drawn to an embodiment of Claim 39 wherein the method further comprises an additional step, namely, separating said mixture into a plurality of groups of molecules.

Shuber et al. teach this/these limitation(s). See, at least, for example, Column 4, beginning at about line 52.

Claim 50 is drawn to an embodiment of Claim 46 wherein the method further comprises an additional step, namely, quantifying a ratio of said first radiolabels to said second radiolabels for each group of molecules.

Shuber et al. teach this/these limitation(s). See, at least, for example, Column 9, beginning at about line 50 - Column 11 at about line 25.

Claim 54 is drawn to an embodiment of Claim 50 wherein the method further comprises an additional step, namely, identifying a group of molecules with a deviated ratio of said first radiolabels to said second radiolabels.

Shuber et al. teach this/these limitation(s). See, at least, for example, Claim 2.

Claim 57 is drawn to an embodiment of Claim 50 wherein the method further comprises an additional step, namely, identifying a unique molecule responsible for causing said deviated ratio of said first radiolabels to said second radiolabel in said group of molecules.

Shuber et al. teach this/these limitation(s). See, at least, for example, Claim 2.

Claim 70 is drawn to a method of analysis which comprises four steps. To begin, molecules in a first sample are labeled with a first radioactive isotope and molecules in a second sample are labeled with a second unique radioactive isotope that is different from said first radioactive isotope. Then, said first sample and said second sample are mixed together to form a mixture Next said mixture is separated into a plurality of fractions. Finally, a fraction with a deviated ratio of radiolabels is identified.

Shuber et al. teach a method of analysis comprising the four steps recited in Claim 70. See, at least, for example, Claim 2.

Claim 71 is drawn to an embodiment of Claim 70 wherein said difference is a quantity of a unique molecule between said two samples.

Shuber et al. teach this/these limitation(s). See, at least, for example, Claim 1.

Claim 72 is drawn to an embodiment of Claim 70 wherein said difference is a modification of a unique molecule between said two samples.

Shuber et al. teach this/these limitation(s). See, at least, for example, Claim 1. Also note that the modification taught by Shuber et al. is a polymorphic variant.

8. **Claim(s) 39, 43-44, 46, 49, 51, 53, 55 and 56** is/are rejected under 35 U.S.C. 102(b) as being anticipated by Sexena [US 4,016,250 (1977)].

Claim 39 is drawn to a method of analysis which comprises three steps. To begin, molecules in a first sample are labeled with a first radioactive isotope. Then, molecules in a second sample are labeled with a second radioactive isotope that is different from said first radioactive isotope. Finally said first sample and said second sample are mixed together

Sexena teach a method of analysis comprising the three steps recited in Claim 39. See, at least, for example, Column 5, beginning at about line 62 - Column 6, at about line 21.

Claim 43 is drawn to an embodiment of Claim 39 wherein the method further comprises two additional steps, namely, quantifying said first radioactive isotope in said mixture and said second radioactive isotope in said mixture.

Sexena teach this/these limitation(s). See, at least, for example, Column 5, beginning at about line 62 - Column 6, at about line 21.

Claim 44 is drawn to an embodiment of Claim 39 wherein all said molecules are proteins.

Sexena teach this/these limitation(s). See, at least, for example, Column 5, beginning at about line 62 - Column 6, at about line 21. Please note that each of the hormones detected by Sexena are proteins.

Claim 46 is drawn to an embodiment of Claim 39 wherein the method further comprises an additional step, namely, separating said mixture into a plurality of groups of molecules.

Sexena teach this/these limitation(s). See, at least, for example, Column 5, - Column 6, beginning at about line 17.

Claim 49 is drawn to an embodiment of Claim 46 wherein the method further comprises two additional steps, namely, a step wherein said first radiolabel in each group of molecules is quantified and a step wherein said second radiolabel in each group of molecules is quantified.

Sexena teach this/these limitation(s). See, at least, for example, Column 11, beginning at about line 24.

Claim 51 is drawn to an embodiment of Claim 49 wherein the method further comprises an additional step, namely, a step wherein a difference between said first sample and said second sample is identified.

Sexena teach this/these limitation(s) wherein this author teaches identifying distinguishable radiolabels (i.e. a difference between said first sample and said second sample).

Claim 53 is drawn to an embodiment of Claim 49 wherein said first radiolabel and said second label are selectively quantified by exploiting the difference in radiation energy between said first radioactive isotope and said second radioactive isotope.

Admittedly Sexena does not explicitly teach this/these limitation(s). However, Sexena does teach the use of a counting device to separately count each isotope in the fractions, see, at least, for example, Column 11, beginning at about line 16. Furthermore, this author teaches using an Auto-gamma counter manufactured by Packard Instrument Co. (Dowers Grove,IL), see, at least, for example, Column 15, beginning at about line 13. Therefore, absent a showing to the contrary the examiner asserts that Sexena teach that said first radiolabel and said second radiolabel are selectively quantified by exploiting the difference in radiation energy between said first radioactive isotope and said second radioactive isotope. For at least the reasons set forth above and set forth above against Claims 39, 46 and 49, Claim 55 is anticipated by Sexena.

Claim 55 is drawn to an embodiment of Claim 53 wherein a screen is used to block a higher proportion of radiation from said first radiolabel than radiation from said second radiolabel.

Admittedly, Sexena do not explicitly teach this/these limitation(s). However, Sexena does teach the use of a counting device to separately count each isotope in the fractions, see, at least, for example, Column 11, beginning at about line 16. Furthermore, this author teaches using an Auto-gamma counter manufactured by Packard Instrument Co. (Dowers Grove,IL), see, at least, for example, Column 15, beginning at about line 13. Absent a showing to the contrary the examiner asserts that the ability of the counting device to separately count each isotope involves the use of the counting device to screen/blocking (i.e. not measure) one radiolabel's emission while measuring the emissions from the second radiolabel. Therefore, for at least the reasons set forth above and set forth above against Claims 39, 46, 49 and 53, Claim 55 is anticipated by Sexena.

Claim 56 is drawn to an embodiment of Claim 53 wherein scintillation counting is used to selectively quantify said first radiolabel and said second radiolabel.

Sexena does not explicitly teach this/these limitation(s). However, Sexena does teach the use of a counting device to separately count each isotope in the fractions, see, at least, for example, Column 11, beginning at about line 16. Furthermore, this author teaches using an Auto-gamma counter manufactured by Packard Instrument Co. (Dowers Grove,IL) which absent a showing to the contrary, the examiner asserts is a scintillation counter. Therefore, for at least the reasons set forth above and set forth above against Claims 39, 46, 49, Claim 53 is anticipated by Sexena.

35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

CLAIM REJECTIONS UNDER 35 USC § 103

10. **Claim(s) 40-42** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. [US 6,203,993 (2001)].

Claim 40 is drawn to an embodiment of Claim 39 wherein the first radioactive isotope is tritium and the second radioactive isotope is carbon-14.

Admittedly, Shuber et al. do not teach a specific embodiment wherein the first radioactive isotope is tritium and the second radioactive isotope is carbon-14. However, these authors do teach using any of a laundry list of radioactive isotopes useful as labels with the caveat that the labels used must be distinguishable one from the other. See, at least, for example, Column 8, beginning at about line 21. Therefore, absent an unexpected result it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method of Shuber et al. wherein tritium is used as the first radioactive isotope and carbon-14 is used as the second radioactive isotope. The motivation to make this modification arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making this obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Claim 41 is drawn to an embodiment of Claim 39 wherein the first radioactive isotope is sulfer -35 and the second radioactive isotope is carbon-14.

This claim is unpatentable over Shuber et al. [US 6,203,993 (2001)] as being *prima facie* obvious for the same reason as applied against Claim 40 above.

Claim 42 is drawn to an embodiment of Claim 39 wherein the first radioactive isotope is phosphorous -33 and the second radioactive isotope is phosphorous -32.

This claim is unpatentable over Shuber et al. [US 6,203,993 (2001)] as being *prima facie* obvious for the same reason as applied against Claim 40 above.

11. **Claim(s) 39-47, 49-51, 53-58, 60, 62-64, 66-73, and 75-78** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. [WO0063701(2000)] in view of Shuber et al. [US 6,203,993 (2001)].

Claim 39 is drawn to a method of analysis which comprises three steps. To begin, molecules in a first sample are labeled with a first radioactive isotope. Then, molecules in a second sample are labeled with a second radioactive isotope that is different from said first radioactive isotope. Finally said first sample and said second sample are mixed together.

Brown et al. (2000) teach a method of analysis comprising the three steps recited in Claim 39 except Brown et al. (2000) teach using different fluorescent labels instead of different radioactive labels as recited in the claim. See at least for example p.18, beginning at line 23- p.20, at about line 19. Please note that Brown et al. do teach using different radioisotopes, see, at least, for example, p.15, beginning at about line 13, but stresses the use of fluorescent labels. However, Shuber et al. do teach two or more different analytes in a single mixture in which said analytes are labeled with different radioactive labels. Note also that Singh et al. [US 2003/0013126 (16 JAN 03)] teach that one of the classical methods to detect multianalytes in an assay is to utilize two different radioisotope labels to distinguish two different analytes. See at least , for example p. 1 [0004]. In view of these findings, it would have been, absent an unexpected result, *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method of Brown et al. (2000) wherein two different radioactive isotopes are used as the labels instead of fluorescent labels. Please note that substitution of one well known method/reagent with known properties for a second well known method/reagent with well known properties would have been *prima facie* obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making this obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Claim 40 is drawn to an embodiment of Claim 39 wherein the first radioactive isotope is tritium and the second radioactive isotope is carbon-14.

Shuber et al. teach using any of a laundry list of radioactive isotope as labels with the caveat that the labels used must be distinguishable one from the other. See, at least, for example, Column 6, beginning at about line 11. Therefore, absent an unexpected result it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method of Brown et al. (2000) wherein tritium is used as the first radioactive isotope and carbon-14 is used as the second radioactive isotope. The motivation to make this modification arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making this obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Claim 41 is drawn to an embodiment of Claim 39 wherein the first radioactive isotope is sulfer -35 and the second radioactive isotope is carbon-14.

Claim 41 would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention over Brown et al. (2000) in view of Shuber et al. for the same reasons as applied against Claim 40 above.

Claim 42 is drawn to an embodiment of Claim 39 wherein the first radioactive isotope is phosphorous -33 and the second radioactive isotope is phosphorous -32.

Claim 42 would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention over Brown et al. (2000) in view of Shuber et al. for the same reasons as applied against Claim 40 above.

Claim 43 is drawn to an embodiment of Claim 39 wherein the method further comprises two additional steps, namely, quantifying said first radioactive isotope in said mixture and said second radioactive isotope in said mixture.

Shuber et al. teach this/these limitation(s). See, at least, for example, Column 5, beginning at about line 11.

Claim 44 is drawn to an embodiment of Claim 39 wherein all said molecules are proteins.

Brown et al. (2000) teach this/these limitation(s). See, at least, for example, Claim 1.

Claim **45** is drawn to an embodiment of Claim 39 wherein the method further comprises an additional step, namely, a step wherein said mixture is contacted with an array.

Brown et al. (2000) teach this/these limitation(s). See, at least, for example, Claim 1.

Claim 46 is drawn to an embodiment of Claim 39 wherein the method further comprises an additional step, namely, separating said mixture into a plurality of groups of molecules.

Both of Brown et al. (2000) and Shuber et al. teach this/these limitation(s). See, at least, for example, Claim 1 of Brown et al. (2000) and Column 5, beginning at about line 11 of Shuber et al.

Claim 47 is drawn to an embodiment of Claim 45 wherein the method further comprises an additional step, namely, a step wherein said first and said second radiolabels are quantified at a spot on said array.

For at least the reasons set forth above against Claim 45 the combination of Brown et al. (2000) in view of Shuber et al. make this embodiment *prima facie* obvious absent of an unexpected result.

Claim 49 is drawn to an embodiment of Claim 46 wherein the method further comprises two additional steps, namely, a step wherein said first radiolabel in each group of molecules is quantified and a step wherein said second radiolabel in each group of molecules is quantified.

For, at least, the reasons set forth above against Claims 39 and 46, the combination of Brown et al. (2000) in view of Shuber et al. make this embodiment *prima facie* obvious absent of an unexpected result.

Claim 50 is drawn to an embodiment of Claim 46 wherein the method further comprises an additional step, namely, a step wherein a ratio of said first radioactive isotope to said second radioactive isotope is quantified.

Brown et al. (2000) teach this limitation wherein the authors teach calculating a ratio of said first label (i.e. Cy5) to said second label (i.e. Cy3). See at least for example, the last paragraph on p.20.

Claim 51 is drawn to an embodiment of Claim 49 wherein the method further comprises an additional step, namely, a step wherein a difference between said first sample and said second sample is identified.

Brown et al. (2000) teach this/these limitation(s). See, at least, for example p.14, beginning at about line 6. Therefore, for at least the reasons set forth above and set forth above against Claims 39, 46 and 49 the combination of Brown et al. (2000) in view of Shuber et al. make this embodiment *prima facie* obvious absent of an unexpected result.

Claim 53 is drawn to an embodiment of Claim 49 wherein said first radiolabel and said second label are selectively quantified by exploiting the difference in radiation energy between said first radioactive isotope and said second radioactive isotope.

Shuber et al. teach this/these limitation(s). See, at least, for example, Column 5, beginning at about line 11. Therefore, for at least the reasons set forth above and set forth above against Claims 39, 46 and 49 the combination of Brown et al. (2000) in view of Shuber et al. make this embodiment *prima facie* obvious absent of an unexpected result.

Claim 54 is drawn to an embodiment of Claim 50 wherein the method further comprises an additional step, namely, identifying a group of molecules with a deviated ratio of said first radiolabels to said second radiolabels.

Shuber et al. teach this/these limitation(s). See, at least, for example, Claim 2.

Claim 55 is drawn to an embodiment of Claim 53 wherein a screen is used to block a higher proportion of radiation from said first radiolabel than radiation from said second radiolabel.

Admittedly, neither Brown et al. (2000) or Schuber et al. explicitly teach this/these limitation(s). However, Shuber et al. do teach the use of a multi-orifice impedence counter, see Column 6, beginning at about line 17, which absent a showing to the contrary functions as a screen used to block one radiolabel's emission while blocking (i.e. not measuring) the emissions from a second radiolabel. Therefore, for at least the reasons set forth above and set forth above against Claims 39, 46, 49 and 53, the combination of Brown et al. (2000) in view of Shuber et al. make this embodiment *prima facie* obvious absent of an unexpected result.

Claim 56 is drawn to an embodiment of Claim 53 wherein scintillation counter is used to selectively quantify said first radiolabel and said second radiolabel.

Shuber et al. teach this/these limitation(s). See, at least, for example, Column 6, beginning at about line 17. Therefore, for at least the reasons set forth above and set forth above against Claims 39, 46, 49 and 53 the combination of Brown et al. (2000) in view of Shuber et al. make this embodiment *prima facie* obvious absent of an unexpected result.

Claim 57 is drawn to an embodiment of Claim 50 wherein the method further comprises an additional step, namely, identifying a unique molecule responsible for causing said deviated ratio of said first radiolabels to said second radiolabel in said group of molecules.

Shuber et al. teach this/these limitation(s). See, at least, for example, Claim 2. In addition, Brown et al. (2000) teach this limitation(s). See, at least, for example, p.14, beginning at about line 6 and p.18, beginning at about line 23 - p.20, at about line 19

Claim 58 is drawn to a method of analysis which comprises four steps. To begin, molecules in a first sample are labeled with a first radioactive isotope and molecules in a second sample are labeled with a second unique radioactive isotope that is different from said first radioactive isotope. Then, said first sample and said second sample are mixed together to form a mixture Next said mixture is contacted with an array. Finally, the ratio of radiolabels is measured at a spot on said array.

Brown et al. (2000) teach a method of analysis comprising the four steps recited in Claim 58 except Brown et al. stresses using different fluorescent labels instead of different radioactive labels as recited in the claim. Please note that Brown et al. (2000) do teach using different radioisotopes, see, at least, for example, p.15, beginning at about line 13, but stresses the use of fluorescent labels. However, Shuber et al. do teach two or more different probes in a single hybridization mixture in which said probes are labeled with different radioactive labels. In view of these findings it would have been, absent an unexpected result, *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method of Brown et al. (2000) wherein two different radioactive isotopes are used as the labels instead of fluorescent labels. Please note that substitution of one well known method/reagent with known properties for a second well known method/reagent with well known properties would have been *prima facie* obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making this obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Claim 60 is drawn to an embodiment of Claim 58 wherein said array is a protein array.

Brown et al. (2000) teach this/these limitation(s). See, at least, for example, p.18, beginning at about line 23 - p.20, at about line 19. Therefore, for at least the reasons set forth above and set forth above against Claim 58, the combination of Brown et al. (2000) in view of Shuber et al. make this embodiment *prima facie* obvious absent of an unexpected result.

Claim 62 is drawn to an embodiment of Claim 58 wherein said difference is a quantity of a unique molecule between the two samples.

Both, Brown et al. (2000) and Shuber et al. teach this/these limitation(s). See, at least, for example, Claim 2 of Shuber et al. and p.14, beginning at about line 6 and p.18, beginning at about line 23 - p.20, at about line 19 of Brown et al. (2000). Therefore, for at least the reasons set forth above and set forth above against Claims 58, the combination of Brown et al. (2000) in view of Shuber et al. make this embodiment *prima facie* obvious absent of an unexpected result.

Claim 63 is drawn to an embodiment of Claim 58 wherein said difference is a modification of a unique molecule between the two samples.

Brown et al. (2000). teach this/these limitation(s). See, at least, for example, p. 16, beginning at about line 32. Therefore, for at least the reasons set forth above and set forth above against Claim 58, the combination of Brown et al. in view of Shuber et al. make this embodiment *prima facie* obvious absent of an unexpected result.

Claim 64 is drawn to an embodiment of Claim 62 wherein said unique molecule is a protein.

Brown et al. teach this/these limitation(s). See, at least, for example, p. 16, beginning at about line 32. Therefore, for at least the reasons set forth above and set forth above against Claim 58 and 63, the combination of Brown et al. (2000) in view of Shuber et al. make this embodiment *prima facie* obvious absent of an unexpected result.

Claim 66 is drawn to an embodiment of Claim 63 wherein said unique molecule is a protein and said modification is a post- translational modification.

Brown et al. (2000) teach this/these limitation(s). See, at least, for example, p. 16, beginning at about line 32. Therefore, for at least the reasons set forth above and set forth above against Claims 58 and 63 , the combination of Brown et al. in view of Shuber et al. make this embodiments *prima facie* obvious absent of an unexpected result.

Claim 67 is drawn to an embodiment of Claim 66 wherein said post- translational modification is phosphorylation.

Brown et al. (2000) teach this/these limitation(s). See, at least, for example, p. 16, beginning at about line 32. Therefore, for at least the reasons set forth above and set forth above against Claim 58, 63 and 66, the combination of Brown et al. (2000). in view of Shuber et al. make this embodiments *prima facie* obvious absent of an unexpected result.

Claim 68 is drawn to an embodiment of Claim 66 wherein said post- translational modification is glycosylation.

Brown et al. (2000) teach this/these limitation(s). See, at least, for example, p. 16, beginning at about line 32. Therefore, for at least the reasons set forth above and set forth above against Claims 58, 63 and 66, the combination of Brown et al. (2000) in view of Shuber et al. make this embodiment *prima facie* obvious absent of an unexpected result.

Claim 69 is drawn to an embodiment of Claim 66 wherein said post- translational modification is a chemical modification.

Brown et al. (2000) teach this/these limitation(s). See, at least, for example, p. 16, beginning at about line 32. Therefore, for at least the reasons set forth above and set forth above against Claims 58, 63 and 66, the combination of Brown et al. (2000) in view of Shuber et al. make this embodiment *prima facie* obvious absent of an unexpected result.

Claim 70 is drawn to a method of analysis which comprises four steps. To begin, molecules in a first sample are labeled with a first radioactive isotope and molecules in a second sample are labeled with a second unique radioactive isotope that is different from said first radioactive isotope. Then, said first sample and said second sample are mixed together to form a mixture Next said mixture is separated into a plurality of fractions. Finally, a fraction with a deviated ratio of radiolabels is identified.

Brown et al. (2000) teach a method of analysis comprising the four steps recited in Claim 70 except Brown et al. (2000) teach using different fluorescent labels instead of different radioactive labels as recited in the claim. Please note that Brown et al. (2000) do teach using different radioisotopes, see, at least, for example, p.15, beginning at about line 13, but stresses the use of fluorescent labels. However, Shuber et al. do teach two or more different probes in a single hybridization mixture in which said probes are labeled with different radioactive labels. In view of these findings it would have been, absent an unexpected result, *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method of Brown et al. (2000) wherein two different radioactive isotopes are used as the labels instead of fluorescent labels. Please note that substitution of one well known method/reagent with known properties for a second well known method/reagent with well known properties would have been *prima facie* obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making this obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Claim 71 is drawn to an embodiment of Claim 70 wherein said difference is a quantity of a unique molecule between said two samples.

Brown et al. (2000) teach this/these limitation(s). See at least, for example, p.14, beginning at about line 6 and p.18, beginning at line 23 - p.20, at about line 19.

Claim 72 is drawn to an embodiment of Claim 70 wherein said difference is a modification of a unique molecule between said two samples.

Brown et al. (2000) teach this/these limitation(s). See at least, for example, p.14, beginning at about line 6. and p.18, beginning at line 23 - p.20, at about line 19.

Claim 73 is drawn to an embodiment of Claim 71 wherein said unique molecule is a protein.

Brown et al. (2000) teach this/these limitation(s). See, at least, for example, p. 16, beginning at about line 32. Therefore, for at least the reasons set forth above and set forth above against Claims 70 and 72, the combination of Brown et al. (2000) in view of Shuber et al. make this embodiment *prima facie* obvious absent of an unexpected result.

Claim 75 is drawn to an embodiment of Claim 72 wherein said unique molecule is a protein and said modification is a post- translational modification.

Brown et al. (2000) teach this/these limitation(s). See, at least, for example, p. 16, beginning at about line 32. Therefore, for at least the reasons set forth above and set forth above against Claims 70 and 72, the combination of Brown et al. (2000) in view of Shuber et al. make this embodiment *prima facie* obvious absent of an unexpected result.

Claim 76 is drawn to an embodiment of Claim 75 wherein said post- translational modification is phosphorylation.

Brown et al. (2000) teach this/these limitation(s). See, at least, for example, p. 16, beginning at about line 32. Therefore, for at least the reasons set forth above and set forth above against Claims 70, 72 and 75, the combination of Brown et al. (2000) in view of Shuber et al. make this embodiment *prima facie* obvious absent of an unexpected result.

Claim 77 is drawn to an embodiment of Claim 75 wherein said post- translational modification is glycosylation.

Brown et al. (2000) teach this/these limitation(s). See, at least, for example, p. 16, beginning at about line 32. Therefore, for at least the reasons set forth above and set forth above against Claims 70, 72 and 75, the combination of Brown et al. in view of Shuber et al. make this embodiment *prima facie* obvious absent of an unexpected result.

Claim 78 is drawn to an embodiment of Claim 75 wherein said post- translational modification is a chemical modification.

Brown et al. (2000) teach this/these limitation(s). See, at least, for example, p. 16, beginning at about line 32. Therefore, for at least the reasons set forth above and set forth above against Claims 70, 72 and 75, the combination of Brown et al. (2000) in view of Shuber et al. make this embodiment *prima facie* obvious absent of an unexpected result.

12. Claim(s) 48, 50 and 61 is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. [WO0063701(2000)] in view of Shuber et al. [US 6,203,993 (2001)] as applied above against Claim 45 and 58 and further in view of Cottrell et al. [US 4,524,275 (1985)].

Claim 48 is drawn to an embodiment of Claim 45 wherein the method further comprises an additional step, namely, a step wherein a magnetic field is applied to said array in order to improve the resolution of detected radiation.

Brown et al. (2000) in view of Shuber et al. reasonably suggest all of the limitations of Claim 48 except these authors do not teach applying a magnetic field in order to improve the resolution of detected radiation. However, as evidenced by Cottrell et al. the use of a magnetic field in order to improve the resolution of detected radiation was well known at the time of the invention. See at least, for example Column 1. In view of these findings, it would have been, absent an unexpected result, *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method of Brown et al. (2000) in view of Shuber et al. wherein a magnetic field is applied to said array in order to improve the resolution of detected radiation. Please note that substitution of one well known method/reagent with known properties for a second well known method/reagent with well known properties would have been *prima facie* obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making this obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Claim 50 is drawn to an embodiment of Claim 46 wherein the method further comprises an additional step, namely, a step wherein a ratio of said first radioactive isotope to said second radioactive isotope is quantified.

Brown et al. (2000) teach this limitation wherein the authors teach calculating a ratio of said first label (i.e. Cy5) to said second label (i.e. Cy3). See at least for example, the last paragraph on p.20. Also note that Cottrell et al. teach quantifying a ratio between two ion beams originating from two distinct isotopes. See, at least, for example, the last paragraph in Column 1 wherein Cottrell et al. teach "in this way the ion beam intensities corresponding to a number of mass to charge ratios can be measured simultaneously, and their values compared directly, so that the ratio between them can be determined accurately even if the absolute value of the intensity of all the beams changes for any reason."

Claim 61 is drawn to an embodiment of Claim 45 wherein the method further comprises an additional step, namely, a step wherein a magnetic field is applied to said array in order to improve the resolution of detected radiation.

Brown et al. (2000) in view of Shuber et al. reasonably suggest all of the limitations of Claim 61 except these authors do not teach applying a magnetic field in order to improve the resolution of detected radiation. However, as evidenced by Cottrell et al. the use of a magnetic field in order to improve the resolution of detected radiation was well known at the time of the invention. See at least, for example Column 1. In view of these findings it would have been, absent an unexpected result, *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method reasonably suggested by the combination of Brown et al. (2000) in view of Shuber et al. wherein a magnetic field is applied to said array in order to improve the resolution of detected radiation. Please note that substitution of one well known method/reagent with known properties for a second well known method/reagent with well known properties would have been *prima facie* obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making this obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

13. **Claim(s) 58-59, 70 and 72** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. [US 5,807,522 (1998)] in view of Shuber et al. [US 6,203,993 (2001)].

Claim 58 is drawn to a method of analysis which comprises four steps. To begin, molecules in a first sample are labeled with a first radioactive isotope and molecules in a second sample are labeled with a second unique radioactive isotope that is different from said first radioactive isotope. Then, said first sample and said second sample are mixed together to form a mixture Next said mixture is contacted with an array. Finally, the ratio of radiolabels is measured at a spot on said array.

Brown et al. (1998) teach a method of analysis comprising the four steps recited in Claim 58 except Brown et al. (1998) stresses using different fluorescent labels instead of different radioactive labels as recited in the claim. Please note that Brown et al. (1998) do teach using standard radioactive detection means, see, at least, for example, Column 13, beginning at about line 33, but stresses the use of fluorescent labels. However, Shuber et al. do teach two or more different probes in a single hybridization mixture in which said probes are labeled with different radioactive labels. In view of these findings, it would have been, absent an unexpected result, *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method of Brown et al. (1998) wherein two different radioactive isotopes are used as the labels instead of fluorescent labels. Please note that substitution of one well known method/reagent with known properties for a second well known method/reagent with well known properties would have been *prima facie* obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making this obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Claim 59 is drawn to an embodiment of Claim 58 wherein said array is a nucleic acid array.

Brown et al. (1998) teach this/these limitation(s). See, at least, for example, Column 13, beginning at about line 47. Therefore, for at least the reasons set forth above and set forth above against Claims 58 and above the combination of Brown et al. (1998) in view of Shuber et al. make this embodiment *prima facie* obvious absent of an unexpected result.

Claim 70 is drawn to a method of analysis which comprises four steps. To begin, molecules in a first sample are labeled with a first radioactive isotope and molecules in a second sample are labeled with a second unique radioactive isotope that is different from said first radioactive isotope. Then, said first sample and said second sample are mixed together to form a mixture Next said mixture is separated into a plurality of fractions. Finally, a fraction with a deviated ratio of radiolabels is identified.

Brown et al. (1998) teach a method of analysis comprising the four steps recited in Claim 70 except Brown et al. teach using different fluorescent labels instead of different radioactive labels as recited in the claim. Please note that Brown et al. do teach using different radioisotopes, see, at least, for example, p.15, beginning at about line 13, but stresses the use of fluorescent labels. However, Shuber et al. do teach two or more different probes in a single hybridization mixture in which said probes are labeled with different radioactive labels. In view of these findings, it would have been, absent an unexpected result, *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method of Brown et al. wherein two different radioactive isotopes are used as the labels instead of fluorescent labels. Please note that substitution of one well known method/reagent with known properties for a second well known method/reagent with well known properties would have been *prima facie* obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making this obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Claim 72 is drawn to an embodiment of Claim 70 wherein said difference is a modification of a unique molecule between said two samples.

Brown et al. teach this/these limitation(s). See at least, for example, p.14, beginning at about line 6. and p.18, beginning at line 23 - p.20, at about line 19.

14. **Claim(s) 63, 65 and 74** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. [US 5,807,522 (1998)] in view of Shuber et al. [US 6,203,993 (2001)] as applied against Claims 58, 63, 70 and 72 above and further in view of Bradley et al. [US 2002/0006623(2002)].

Claim 63 is drawn to an embodiment of Claim 58 wherein said difference is a modification of a unique molecule between the two samples.

Brown et al. (1998) in view of Shuber et al. reasonably suggest a method of analysis comprising all of the limitations of Claim 63 except these authors do not explicitly teach detecting a difference between two samples wherein said difference is a modification of a unique molecule. However, Bradley et al. do teach using nucleic acid arrays to detect methylated DNA. (i.e. Bradley et al. teach detecting a difference between two samples wherein said difference is a modification of a unique molecule.) See at least for example, paragraph [0113] Therefore, it would have been, absent an unexpected result, *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method reasonably suggested by the combination of Brown et al. (1998) in view of Shuber et al. wherein methylated DNA is detected as suggested by Bradley et al. The motivation to make this modification comes from Bradley et al. who teach "Generating a molecular profile of a nucleic acid sample by the analysis of differential methylation and CpG islands using methods and arrays of the invention can be practiced with methods and compositions known in the art."

Claim 65 is drawn to an embodiment of Claim 63 wherein said unique molecule is DNA and said modification is a methylation.

Brown et al. (1998) in view of Shuber et al. teach all of the limitations of Claim 65 except these authors do not teach detecting methylated DNA. However, Bradley et al. do teach using nucleic acid arrays to detect methylated DNA. See at least for example, paragraph [0113] Therefore, it would have been, absent an unexpected result, *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method reasonably suggested by the combination of Brown et al. (1998) in view of Shuber et al. wherein methylated DNA is detected as suggested by Bradley et al. The motivation to make this modification comes from Bradley et al. who teach "Generating a molecular profile of a nucleic acid sample by the analysis of differential methylation and CpG islands using methods and arrays of the invention can be practiced with methods and compositions known in the art."

Claim 74 is drawn to a method of analysis which comprises four steps. To begin, molecules in a first sample are labeled with a first radioactive isotope and molecules in a second sample are labeled with a second unique radioactive isotope that is different from said first radioactive isotope. Then, said first sample and said second sample are mixed together to form a mixture Next said mixture is separated into a plurality of fractions. Finally, a fraction with a deviated ratio of radiolabels is identified.

Brown et al. teach a method of analysis comprising the four steps recited in Claim 70 except Brown et al. teach using different fluorescent labels instead of different radioactive labels as recited in the claim. Please note that Brown et al. do teach using different radioisotopes, see, at least, for example, p.15, beginning at about line 13, but stresses the use of fluorescent labels. However, Shuber et al. do teach two or more different probes in a single hybridization mixture in which said probes are labeled with different radioactive labels. In view of these findings it would have been, absent an unexpected result, *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method of Brown et al. wherein two different radioactive isotopes are used as the labels instead of fluorescent labels. Please note that substitution of one well known method/reagent with known properties for a second well known method/reagent with well known properties would have been *prima facie* obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making this obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

CLAIM OBJECTIONS

15. **Claim(s) 52** is /are is objected to because it/they is/are dependent upon a rejected independent base claim, however, these claims would appear to be allowable over the prior art if rewritten to overcome the rejection(s) under 35 U.S.C. 112 set forth in this Office action and/or to include all of the limitations of the base claim and any intervening claims.

CONCLUSION

16. **Claim(s) 39-78** is/are rejected and/or objected to for the reason(s) set forth above.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ethan Whisenant, Ph.D. whose telephone number is (571) 272-0754. The examiner can normally be reached Monday-Friday from 8:30AM -5:30PM EST or any time via voice mail. If repeated attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached at (571) 272-0745.

The fax number for this Examiner is (571) 273-0754. Before faxing any papers please inform the examiner to avoid lost papers. Please note that the faxing of papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

ETHAN WHISENANT
PRIMARY EXAMINER
Art Unit 1634

Search Notes

02 APR 05

Databases searched: USPATFULL, USPGPUBS and EUROPATFULL via EAST, CAplus, Medline

Search terms:

Inventor(s) : e.g. Tran N?/au

Different radioactive labels or different radiolabel? or Different radioactive isotopes

Protein? and/or Protein analysis or nucleic or oligonuc$

Array?

Hybridization

Binding

Phosphorylation or glycosylation or post translational modification or methylation

Half Life

Deviated ratio